K051072

MAY 12 2005

Section E

510(k) Summary of Safety and Effectiveness

For

VARIANT™ nbs Sickle Cell Program

510(k) Summary of Safety and Effectiveness

Submitter

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Preparation Date

March 17, 2005

New device Name

Trade Name:	Bio-Rad VARIANT™nbs Sickle Cell Program
Common Name:	Hemoglobin F, A, S, D, C and E Determination by HPLC
Classification Name:	Abnormal Hemoglobin Quantitation (21 CFR 864.7415)

Predicate Device Name

Trade Name:	Bio-Rad VARIANT™ Sickle Cell Short Program
Classification Name:	Abnormal Hemoglobin Quantitation (21 CFR 864.7415)
Applicant:	Bio-Rad Laboratories, Inc.
510(k) Number:	K924813

Indications for Use Statement and Intended Uses

The Bio-Rad VARIANTnbs Sickle Cell Program is intended as a qualitative screen for the presence of hemoglobins F, A, S, D, C and E in eluates of neonatal blood collected on filter paper by high performance liquid chromatography (HPLC).

The Bio-Rad VARIANTnbs Sickle Cell Program is intended for Professional Use Only. For In Vitro Diagnostic Use.

The Bio-Rad VARIANTnbs Sickle Cell Program is for use only with the Bio-Rad VARIANTnbs Newborn Screening System.

New Device Description

The VARIANTnbs Newborn Screening System is a High Performance Liquid Chromatography (HPLC) system consisting of an auto sampler for microwell plates (VARIANTnbs Neonatal Auto Sampler) and a chromatography station (VARIANTnbs Neonatal Chromatography Station). The VARIANTnbs Sickle Cell Program is a reagent kit that includes an analytical cartridge containing cation exchange resin and two (2) buffers for establishing a gradient. The Genetic Data Management (GDM) software is designed to execute the VARIANTnbs Sickle Cell Program on the VARIANTnbs Newborn Screening System for the purposes of qualitatively screening for the presence of normal hemoglobins F and A and abnormal hemoglobins S, D, C and E in eluates of discs punched from neonatal heel stick blood collected on filter paper. Eluted samples are aspirated directly from microwell plates with the filter paper disc still present, collected in a sample loop and then injected into the flow path of the chromatography module. The hemoglobins of interest are retained on the analytical cartridge in the presence of Elution Buffer 1. The ionic strength is subsequently raised by adding increasing amounts of Elution Buffer 2. The pre-programmed gradient is designed to have the hemoglobins of interest elute from the cartridge with retention times that fall within pre-determined windows characteristic of known hemoglobins. Eluted hemoglobins are detected with a dual-wavelength filter photometer which monitors hemoglobin absorbance at 415 nm and corrects for any gradient induced absorbance changes at 690 nm. Processed data is output in a printed report that contains 1) sample identification, 2) date and time of analysis, 3) a peak table containing observed peak name(s), retention time(s), peak height(s), peak area(s), and relative area percent(s), 4) total chromatogram area, 5) chromatogram and 6) any error message(s). Also reported is an optional "pattern assignment" based upon "pattern rules" derived from literature.

Comparison with Predicate Device

Summary of Technological Characteristic Similarities to Predicate Device		
Features	New Device: Bio-Rad VARIANT™nbs Sickle Cell Program	Predicate Device: Bio-Rad VARIANT™ Sickle Cell Short Program (K#924813)
Intended Use	The Bio-Rad VARIANTnbs Sickle Cell Program is intended as a qualitative screen for the presence of hemoglobins F, A, S, D, C and E in eluates of neonatal blood collected on filter paper by high performance liquid chromatography (HPLC).	The VARIANT Sickle Cell Short Program is designed as a qualitative screen for the presence of hemoglobins F, A, S, D, C and E in eluates of neonatal blood collected on filter paper by high performance liquid chromatography.
	For In Vitro Diagnostic Use.	For In Vitro Diagnostic Use.
	For Professional Use Only.	For Professional Use Only.
Target Population	Neonates.	Neonates.
Design – Assay principle	Cation exchange high performance liquid chromatography.	Cation exchange high performance liquid chromatography.
Design – Assay Detection	Heme absorbance at 415 nm with background correction at 650 nm.	Heme absorbance at 415 nm with background correction at 650 nm.
Design – Analytes Identified	Six retention time windows for hemoglobins F, A, E, D, S and C.	Six retention time windows for hemoglobins F, A, E, D, S and C.
Design – Sample Type	Neonatal dried blood spots on filter paper collection cards.	Neonatal dried blood spots on filter paper collection cards.
Design – Punched Disc	One 1/8" disc.	One 1/8" disc.

Summary of Technological Characteristic Similarities to Predicate Device		
Features	New Device: Bio-Rad VARIANT™nbs Sickle Cell Program	Predicate Device: Bio-Rad VARIANT™ Sickle Cell Short Program (K#924813)
Design – Manual Worklists	Accepts manual worklists.	Accepts manual worklists.
Materials - Components	Elution Buffer 1. Elution Buffer 2. Wash Solution. Analytical Cartridge. Lyophilized Whole Blood Primer. Lyophilized Retention Time Marker 1 (FAES). Lyophilized Retention Time Marker 2 (FADC).	Elution Buffer 1. Elution Buffer 2. Wash Solution. Analytical Cartridge. Lyophilized Whole Blood Primer. Lyophilized Retention Time Marker 1 (FAES). Lyophilized Retention Time Marker 2 (FADC).
Performance – Precision	Peak retention time precision is <1% for all hemoglobin peaks.	Peak retention time precision is <1% for all hemoglobin peaks.
Compatibility with Environment	U.S. FCC EMI and E.U. EMC standard compliant.	U.S. FCC EMI and E.U. EMC standard compliant.
Human Factors	For in vitro diagnostic use. For professional use only.	For in vitro diagnostic use. For professional use only.
Energy Used	Auto-switching 110 V and 220 V.	110 V and 220 V models.
Chemical Safety	Sodium azide concentration <0.05%. Gentamicin Sulfate concentration <0.1%. Tobramycin concentration <0.1%. Warnings provided in labeling as required, including State of California Proposition 65 Warning.	Sodium azide concentration <0.05%. Gentamicin Sulfate concentration <0.1%. Tobramycin concentration <0.1%. Warnings provided in labeling as required, including State of California Proposition 65 Warning.
Electrical, Mechanical and Thermal Safety	System certification to US and Canadian product safety standards and EU low voltage safety standards.	System certification to US and Canadian product safety standards and EU low voltage safety standards.
Standards Met	• EN375:2002 • EN591:2001 • EN980:2003 • EN1658:1996 • EN13485:2003 • EN13640:2002 • EN14971:2001 • EN61010-1:2001 • EN61010-2-101:2002 • EN61326:2001	• EN375:2002 • EN591:2001 • EN980:2003 • EN1658:1996 • EN13485:2003 • EN13640:2002 • EN14971:2001 • EN61010-1:2001 • EN61010-2-101:2002 • EN61326:2001

Summary of Technological Characteristic Differences in Comparison to Predicate Device		
Features	New Device: Bio-Rad VARIANT™nbs Sickle Cell Program	Predicate Device: Bio-Rad VARIANT™ Sickle Cell Short Program (K#924813)
Design – System Configuration	Separate chromatography and auto sampler modules and separate PC workstation with software.	Single integrated unit with chromatography, auto sampler and software functionalities.
Design – Media	CD-ROM.	ROM Card.

Summary of Technological Characteristic Differences in Comparison to Predicate Device		
Features	New Device: Bio-Rad VARIANT™nbs Sickle Cell Program	Predicate Device: Bio-Rad VARIANT™ Sickle Cell Short Program (K#924813)
Design – Container, Elution Volume, Reconstitution Volume, Sample Loop, Column loading	Plastic 96 microwell plate. 250 µL sample elution volume. 500 µL primer and retention time marker reconstitution volume. 10 µL sample loop. Column loading is 1/25 of eluted sample volume and 1/50 of reconstituted material.	Plastic sample vial. 500 µL sample elution volume. 1000 µL primer and retention time marker reconstitution volume. 20 µL sample loop. Column loading is 1/25 of eluted sample volume and 1/50 of reconstituted material.
Design – Aspiration Probe Tip, Punched Disc Disposition	Beveled aspiration probe tip. Dried blood spot punched disc left in microwell during sample aspiration.	Blunt aspiration probe tip. Dried blood spot punched disc removed before sample aspiration.
Design – Additional retention time windows.	Seven (7) additional retention time windows: F1, "Other (1)", "Other (2)", "Other (3)", "Other (4)", "Other (5)" and "Other (6)".	Feature not available.
Design – Automated Worklists	Accepts automated worklists from spot punchers.	Feature not available.
Design – Pattern Assignment	Optional pattern assignment feature uses pattern rules derived from literature.	Feature not available.
Performance – Variants Limit of Detection	The limit of detection for S, D, C and E is 1% of the total area of the sample when the total area is 1.5 million microvolt·second.	Limit of detection for hemoglobins S, D, C and E is 1% of the total area when the total area of the sample is 1.0 million microvolt·second.
Performance – Guideline for Interpretation of Results	Total area must be between 900,000 to 6.3 million microvolt·second.	Total area should range from 1,000,000–3,000,000 microvolt·second.
Performance – Total Area Limit of Detection	900,000 microvolt·second.	Not addressed in instruction manual.
Performance – Bilirubin interference	Bilirubin up to 20 mg/dL does not interfere.	Not addressed in instruction manual.
Performance – Triglyceride interference	Triglyceride up to 6000 mg/dL does not interfere.	Not addressed in instruction manual.
Performance - Eluate stability	Eluates are stable for 48 hrs on the cooled auto sampler and at 2-8 °C and stable for 24 hrs at 15-30 °C.	Eluates are stable for 24 hrs at 2-8 °C.
Guidances Met	• FDA 2002 - General Principles of Software Validation; Final Guidance for Industry and FDA Staff. • FDA 1999 - Guidance for Off-the-Shelf Software Use in Medical Devices; Final. • FDA 1998 - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; Final. • FDA 2003 – Device Advice; Content of a 510(k)	Not addressed.
Standards Met	• NCCLS EP-05A 1999. • NCCLS EP-05A2 2004.	Not addressed.

Testing to Establish Equivalence

- **Correlation**

Method correlation between predicate device and Bio-Rad VARIANT™nbs Sickle Cell Program new device was evaluated using 1025 samples prepared from neonatal dried blood spot collection cards. The results are presented in the following table:

Hemoglobin Identification Correlation Summary				
	Number of Samples	Predicate Device	New device	
		F, A, E, D, S and (or) C Identified	Agree	Disagree
	591	FA	590	1 (FAS)
	52	FAE	52	0
	38	FAD	37	1 (FADC)
	247	FAS	247	0
	90	FAC	90	0
	3	FSC	3	0
	2	FC	2	0
	1	FE	1	0
	1	F	1	0
Total	1025		1023	2

- **Precision**

The Bio-Rad VARIANT™nbs Sickle Cell Program new device retention time precision protocol was based on NCCLS Protocol EP5-A (Vol. 19, No. 2) and EP5-A2 (Vol. 24, No. 25). Two analytical runs were performed per day on 20 days for a total of 40 runs on each of 3 separate systems. Each run included 4 replicates of two retention time positional QC controls. Within-run precision and within-device precision (formerly total precision) were determined. The reported predicate device retention time precision protocol included the same two retention time positional QC controls, however, the protocol did not conform to NCCLS Protocol EP5-A2 guidelines nor was with-in laboratory (or within-device) precision reported. The results are presented in the following tables:

Retention Time With-in Run Precision Summary								
Device	Replicates	Sample	Retention Time Within-Run Precision (CV %)					
			Peak F	Peak A	Peak E	Peak D	Peak S	Peak C
New	160 x 3	QC Control 1	0.3–0.5	0.3-0.4	0.3-0.4		0.2-0.3	
Predicate	10 x 1	QC Control 1	0.7	0.0	0.0		0.0	
New	160 x 3	QC Control 2	0.3–0.5	0.3-0.4		0.2-0.3		0.1-0.3
Predicate	10 x1	QC Control 2	0.6	0.0		0.4		0.3

Retention Time With-in Device Precision (Formerly Total Precision)								
Device	Replicates	Sample	Retention Time Within-Device Precision (CV %)					
			Peak F	Peak A	Peak E	Peak D	Peak S	Peak C
New	160 x 3	QC Control 1	0.3–0.6	0.4-0.6	0.4-0.6		0.5-0.6	
Predicate	Not reported							
New	160 x 3	QC Control 2	0.3–0.7	0.4-0.6		0.4-0.5		0.2-0.3
Predicate	Not reported.							

Variant Peak Area Limit of Detection

The Bio-Rad VARIANT™nbs Sickle Cell Program new device peak area limit of detection for hemoglobin variants (E, D, S and C) was determined using a total of 102 sample measurements bracketing the 1% peak area limit of detection for each variant when the total chromatogram area was 1.5 million microvolt·second. The reported predicate device peak area limit of detection was 1% when the total chromatogram area was 1.0 million microvolt·second. The results are presented in the following table:

Variant Peak Area Limit of Detection					
Device	Chromatogram Total Area (microvolt·second)	Peak Area% Limit of Detection			
		Peak E	Peak D	Peak S	Peak C
New	1.5	1%	1%	1%	1%
Predicate	1.0	1%	1%	1%	1%

Conclusions

The similarities of the intended use and the general performance characteristics and results of the newly described and evaluated Bio-Rad VARIANT™nbs Sickle Cell Program new device used with the Bio-Rad VARIANT™nbs Newborn Screening System with Bio-Rad Genetic Data Management Software for the VARIANT™nbs Newborn Screening System are nearly identical to logical extensions of those for the cleared predicate device and associated system. Thus, one may conclude based on the new device system use of the same HPLC technology, and the nearly equivalent results obtained from the correlation, precision and variant peak area limit of detection versus the corresponding results obtained with the predicate device system that the new Bio-Rad VARIANT™nbs Sickle Cell Program system is substantially equivalent to the cleared and currently marketed predicate device system.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY 12 2005

Bio-Rad Laboratories
c/o Dr. Alfredo J. Quattrone
California Department of Health Services (CA-DHS)
Food and Drug Branch, MS-7602
1500 Capitol Avenue
Sacramento, CA 95814

Re: k051072
Trade/Device Name: Bio-Rad VARIANT™ nbs Sickle Cell Program
Regulation Number: 21 CFR 864.7415
Regulation Name: Abnormal hemoglobin assay
Regulatory Class: Class II
Product Code: GKA
Dated: April 19, 2005
Received: April 26, 2005

Dear Dr. Quattrone:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240) 276-0484. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html

Sincerely yours,

Robert L. Becker, Jr., MD, Ph.D
Director
Division of Immunology and Hematology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Statement of Indications for Use

510(k) Number if Known: K051072

Device Name: **Bio-Rad VARIANT™nbs Sickle Cell Program**

Indications for Use:

The Bio-Rad VARIANTnbs Sickle Cell Program is intended as a qualitative screen for the presence of hemoglobins F, A, S, D, C and E in eluates of neonatal blood collected on filter paper by high performance liquid chromatography (HPLC).

The Bio-Rad VARIANTnbs Sickle Cell Program is intended for Professional Use Only. For In Vitro Diagnostic Use.

The Bio-Rad VARIANTnbs Sickle Cell Program is for use only with the Bio-Rad VARIANTnbs Newborn Screening System.

Prescription Use ✓ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K051072